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DOI:

[10.1177/0269881117714047](https://doi.org/10.1177/0269881117714047)

*Document Version*

Peer reviewed version

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*Citation for published version (APA):*

Huang, K-L., Fang, C-J., Hsu, C-C., Wu, S-I., Juang, J. JM., & Stewart, R. (2017). Myocardial infarction risk and antipsychotics use revisited: a meta-analysis of 10 observational studies. *Journal of Psychopharmacology*, 31(12), 1544-1555. <https://doi.org/10.1177/0269881117714047>

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**Title:**

Myocardial infarction risk and antipsychotics use revisited: a meta-analysis of 10  
observational studies

**Short running title:**

Myocardial infarction risk and antipsychotic agents

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## **Abstract**

**Objective:** Associations between antipsychotic agent (AP) use and myocardial infarction (MI) risk have been inconsistent and remain controversial. We therefore conducted a meta-analysis of observational studies to address this knowledge gap.

**Method:** Detailed electronic database searches were performed to identify reports of observational studies that evaluated the association between AP use and the risk of MI. Pooled odds ratios were calculated using random or fixed-effects models.

**Results:** In total, 4 case-control studies, 2 case-crossover studies, 1 case-case time control study, 3 cohort studies, and 1 self-controlled case series were included. The pooled odds ratio (95% CIs) between any AP use and MI risk was 1.55 (1.33-1.79) compared with non-use: 1.39 (1.06-1.82) for atypical AP use and 1.57 (1.29-1.91) for typical AP use. Subgroup analyses indicated that male gender, schizophrenia diagnosis and AP exposure periods  $\leq 60$  days, but not prior cardiovascular disease diagnosis or older age, were associated with higher risk of MI.

**Conclusion:** Current evidence, based on 10 observational studies, suggested that AP use might be a potential risk factor of MI. However, we cannot conclude at this time due to significant heterogeneity among studies. We suggest that, instead of not using APs in fear of the risk, careful cardiovascular monitoring before and during AP treatment in high-risk patients group is needed. Additional high-quality prospective

studies are required to evaluate the association between APs and the risk of MI.

### **Keywords**

Antipsychotic agents, myocardial infarction, meta-analysis, schizophrenia, serious  
mental illness

## Introduction

Antipsychotic agents (APs) are first-line medication treatment for schizophrenia. They effectively reduce symptoms and behaviors associated with the disorder. In an 11-year follow up study of schizophrenia patients, long term exposure (7-11 years) to AP treatment was associated with around a 20% lower mortality than those without medication use (Tiihonen et al., 2009). The use of APs is widespread, but accumulating data started to indicate that these agents might correlate with cardiovascular risk.(Ray et al., 2009; Enger et al., 2004). The mechanism for this effect has yet to be fully clarified. APs may induce glucose or metabolic dysfunctions (Deng, 2013), QT interval prolongation, ventricular arrhythmia (Polcwiartek et al., 2016), ischemic stroke (Sacchetti et al., 2010) and thereby increase cardiovascular risk (Scigliano and Ronchetti, 2013). However, the evidence for increased MI risk associated with the use of APs is conflicting. Some studies have reported an increased risk of MI associated with APs (Pratt et al., 1996; Thorogood et al., 1992; Enger et al., 2004), whereas others have found no such association (Jerrell and McIntyre, 2007; Nakagawa et al., 2006). Methodological limitations and heterogeneous clinical settings have hindered conclusive findings (Brauer et al., 2011). Thus, further studies are needed to examine the associations.

Few meta-analyses have been conducted examining the risk of MI associated with the use of APs. A meta-analysis of observational studies found that older patients (> 80 years) using typical APs were at higher risk for MI [relative risk (RR) = 1.2, 95% CIs: 1.16-1.23] compared to atypical AP users (Jackson et al., 2014);however, this only identified two cohort studies. Another meta-analysis found a 1.88-fold higher likelihood [odds ratio (OR) = 1.88, 95% CIs: 1.39-2.54] of MI in AP users vs. non-users (Yu et al., 2016). More pronounced MI risk (OR 2.64, 95% CIs 2.48-2.81)

was found in short-term users. Among, the nine studies they identified, only two (Brauer et al., 2015; Pariente et al., 2012) provided separate estimates for different time windows after AP initiation. Besides, a more recently published study (Hwang et al., 2014) was not included in their meta- analysis. It is widely recognized that systematic reviews of randomized controlled trials (RCTs) represent the most reliable and appropriate reference standard to address questions of effectiveness, as they are designed to minimize bias. But for rare and adverse events, such as MI, systematic reviews of observational studies are the main source of evidence because RCTs tend to have insufficient sample size (even when combined) and generalizability to real-world practice. As there have been no RCTs investigating the occurrence of MI when taking APs, we performed a comprehensive meta-analysis of all observational studies to date to address this knowledge gap.

## **Methods**

This review was reported according to PRISMA guidelines (Moher et al., 2009).

### **Search strategy**

The eight databases searched for this study comprised Medline (Ovid), EMBASE, CENTRAL, PsycINFO, Psychology and Behavioral Sciences Collection (PBSC), CINAHL, Iowa Drug Information Service (IDIS), and Index to Taiwan Periodical Literature System (all from inception to the end of June 2016), and a supplementary search in TRIP Database and Google Scholar. References provided in the selected studies and systematic reviews were further checked for additional citations of published or unpublished reports. E-mail alerts were established to identify newly

released studies from the databases that fell within the scope of our review.

The keywords used in the search were antipsychotic agents and myocardial infarction. The search strategy included free-text and controlled vocabulary terms (e.g. Medical Subject Headings) for these topics. No language restrictions were applied. On the basis of the MEDLINE (Ovid) search strategy, queries were revised to perform the best searches in the other databases. The MEDLINE (Ovid) search strategy is shown in Table S2.

### Eligibility criteria

We included studies that met all of the following criteria: (1) observational design (eg. case-control or cohort studies); (2) evaluation of the association between AP use and the risk of myocardial infarction (MI); (3) comparing APs to a non-user reference group; (4) direct reporting of RR, OR, or hazard ratio (HR) with corresponding 95% CIs; (5) using statistical adjustments for potential confounders. We excluded studies evaluated patients with dementia due to unlicensed indication.

Two authors (KLH and CCH) independently selected the trials based on the above criteria, and disagreements were resolved by a third author (SIW). Included studies were then assessed for quality using the nine-star Newcastle-Ottawa Scale (NOS)(Wells et al., 2008). The rating was also performed by two evaluators, and discrepancies were resolved by a third evaluator, as was study selection. Low quality was defined as an NOS score below the average value for the included studies, and high quality as an NOS score at or above the average.

### Data extraction



KLH and CCH extracted the data independently, with disagreements resolved through discussion and consensus with other team members. For each trial, data related to the characteristics of the trial and the reported results were extracted. The following data were collected: study name, study design, country, study period, characteristics of study population, definition of AP use, adjusted OR,RR or HR with 95% CIs, ascertainment of AP use, ascertainment of MI and variables adjusted for in the analysis. For studies that applied different models for the calculation of estimate risks, results adjusted with more potential confounders were chosen.

### Statistical analysis

Review Manager (RevMan) Version 5.3 (The Nordic Cochrane Centre, 2014)

software was used for data analysis. Adjusted data (adjusted OR,RR or HR with 95% CIs) were used for the meta-analysis. Given that the outcome of interest was rare, we assumed equivalence of the OR, RR and HR. Studies were combined by using the inverse variance method. Pooling was performed in both fixed and random-effect models. Heterogeneity was assessed with the  $I^2$  index and Cochran's  $Q$  ( $X^2$ ) statistics. We considered an  $I^2$  value greater than 50% and  $p \leq 0.10$  as indicative of heterogeneity. For the  $I^2$  metric, low, moderate, and high values were considered to be

25%, 50%, and 75%, respectively. If the  $I^2$  index showed significant heterogeneity between the study results, a random-effect model was used. We also performed subgroup meta-analyses based on the following: i) type of study design (case-control, case-crossover, or cohort study); ii) quality of study methodology; iii) gender; iv) age (<50 years, 50-69 years, >70 years); v) dementia or schizophrenia population; vi) time window after initiation of APs ( $\leq 30$  days,  $\leq 60$  days or >90 days); vii) presence or absence of prior cardiovascular disease (CVD). Sensitivity analyses were employed to find potential origins of heterogeneity and to examine the influence of various exclusions on the combined OR. The funnel plot approach was used to investigate publication bias.

## **Results**

### **Study selection**

Of 1783 potentially relevant articles identified in the literature search, titles and abstracts of 1488 were examined and excluded by the consensus of two authors. In cases of discordant exclusions, a third author made the final selection. Thus, 26 full-text manuscripts were retrieved for detailed evaluation. Of these, 15 were excluded for the following reasons: three because they were review articles (Brauer et

al., 2011; Feinstein, 2002; Ottervanger et al., 1997); one because its psychotropic drugs did not include antipsychotic agents (Lapane et al., 1995); three because they used risperidone or aripiprazole as the reference group (Citrome et al., 2013; Pasternak et al., 2014; Sahlberg et al., 2015); six because they used typical or atypical APs as the reference group (Murray-Thomas et al., 2013; Vasilyeva et al., 2013; Huybrechts et al., 2012; Kleijer et al., 2012; Mehta et al., 2011; Wang et al., 2009); two because they did not use adjusted OR or RR (Barak et al., 2007; Jerrell and McIntyre, 2007); and one because they included dementia patients only (Pariente et al., 2012). Ten studies were thus retained for full data extraction for the meta-analysis. Figure 1 summarizes the literature search flow.

### Study characteristics

Table 1-1, 1-2 and 1-3 summarizes the characteristics of the studies included in the meta-analysis. One studies (Brauer et al., 2015; Pariente et al., 2012) analyzed two different types of study design: Brauer et al. (2015) used the self-controlled case series and case-control study design to investigate the association between MI risk and AP use. We found four case-control studies (Brauer et al., 2015; Nakagawa et al., 2006; Penttinen and Valonen, 1996; Thorogood et al., 1992), two case-crossover

studies (Wu et al., 2015b; Lin et al., 2014), one case-case time control study (Wang, 2011), Threecohort studies (Enger et al., 2004; Hwang et al., 2014; Pariente et al., 2012; Pratt et al., 1996) and oneself-controlled case series(Brauer et al., 2015; Pariente et al., 2012). The countries where the studies had been performed were Finland, Denmark, UK, Canada, Taiwan, and USA,and the range of study enrolment periods was 1980-2012. Eight studies included both males and females, one study was male only (Penttinen and Valonen, 1996) and one study female only(Thorogood et al., 1992). The studies included were similar in terms of ascertainment of AP use and MI, mainly reliant on prescription data and diagnostic codes. Three studies (Thorogood et al., 1992; Penttinen and Valonen, 1996; Pratt et al., 1996) evaluated exposure to APs and the risk of MI by interview and from patients' records. It should be borne in mind that studies conducted before 1996 (Penttinen and Valonen, 1996; Pratt et al., 1996; Thorogood et al., 1992)provided information only on typical AP use,and the doses of typical agents may have been higher than currently. Table 2 shows the methodological quality of included studies. The mean NOS score was 7.2 for the 10 studies (range: 5-9).

Association between antipsychotic use and the risk of myocardial infarction

The multivariable-adjusted ORs of MI associated with antipsychotic use in individual studies and summary estimates are shown in Figure 2. Overall, the use of any antipsychotic agent was associated with a significantly increased risk of MI (OR 1.55, 95% CIs 1.33-1.79), but a high heterogeneity was detected ( $P < 0.10$ ;  $I^2 = 97\%$ ). In a subgroup meta-analysis by study design, an increased MI risk with antipsychotic use was observed in case-crossover studies (OR 2.41, 95% CIs 2.21-2.64;  $I^2 = 51\%$ ). Table 3 shows the results of subgroup meta-analyses. In the subgroup meta-analyses according to study quality, significant associations of antipsychotic use and increased risk of MI were observed among high quality studies (OR 1.42, 95% CIs 1.21-1.66), and among low quality studies (OR 3.08, 95% CIs 1.84-5.15). Use of atypical and typical APs were associated with significantly increased odds of MI (OR 1.39, 95% CIs 1.06-1.82; OR 1.57, 95% CIs 1.29-1.91, respectively). No significant differences were found in people with use of these agents in both. Increased risk of MI was observed in both genders (male: OR 2.83, 95% CIs 2.60-3.08; female: OR 2.26, 95% CIs 1.36-3.77), and in patients with schizophrenia (OR 2.25, 95% CIs 1.98-2.55).

Higher MI risk was observed in the initial 60 days of exposure to antipsychotic agents ( $\leq 30$  days: OR 2.33, 95% CIs 2.02-2.69;  $\leq 60$  days: OR 2.11, 95% CIs 1.85-2.40), with ORs decreasing over time ( $\leq 90$  days: OR 1.56, 95% CIs

1.28-1.91). The risk of MI appeared not to be increased in elderly or in patients with or without prior CVD diagnoses.

### **Sensitivity analyses and publication bias**

First, specific studies were excluded to further evaluate the reliability and stability of our conclusions. We excluded studies from the same database, and studies with two study designs. Secondly, the leave-one-out analysis was performed by omitting one study in turn. The positive association was not substantially changed in any of these analyses. Robust results are displayed in Table 4. Visual inspection of the funnel plot showed asymmetry. Thus publication bias was observed.

### **Discussion**

The aim of this meta-analysis was to assess the risk of MI amongst users of typical and atypical APs compared with non-users. Our review included case-control, case-crossover, case-case time control, cohort, and self-controlled case series studies. Findings suggest the risk of MI is increased generally in AP users compared to non-users, with a pooled OR estimate of 1.55 (95% CIs 1.33-1.79). In the subgroup meta-analyses, MI risk appears to be greater in case-crossover studies, in male genders, in patients with schizophrenia, and during the first 2 months of APs use.

Our results were consistent with a previous meta-analysis (Yu et al., 2016).

However, our review identified two additional studies (Wang, 2011; Hwang et al., 2014) and pooled all risk estimates. Studies conducted before 2006 (Thorogood et al. 1992, Penttinen and Valonen 1996, Pratt et al. 1996, Enger et al. 2004) were rated as low quality based on NOS scores. Higher MI risk was observed among low quality studies compared with high quality studies. Higher doses of typical agents were prescribed at these earlier years compared to current usual practice, and might cause an overestimation on the MI risk. Enger et al. (2004) indicated that AP users in patients with schizophrenia had increased risk for MI, compared to controls. The higher MI risk observed in APs users with schizophrenia could partly be explained by the unhealthy lifestyle (e.g., smoking, lack of exercise and obesity). Some studies (Lin et al., 2010; Wu et al., 2015a) have found that people with schizophrenia have a higher risk of MI compared to the general population. Besides, Osborn et al. (2007) reported that people with severe mental illness who were not prescribed any APs remained at increased risk of coronary heart disease (CHD) than controls, whereas those prescribed such agents were at even greater risk.

Our findings of elevated risk for MI in short term APs users are also consistent with those from previous studies (Brauer et al., 2015; Lin et al., 2014; Pariente et al., 2012; Yu et al., 2016), where the incidence rate of MI has been found to be higher during the

first two months of treatment, declining with longer exposure time and potentially related to AP tolerance and cross-tolerance (Lin et al., 2014; Yu et al., 2016). Another explanation for such possibility might be that the indication for which APs were prescribed (e.g., acute psychotic phase in schizophrenia) was associated with state dependent cardiovascular risk factors (e.g., agitation), which then being controlled (e.g., because of AP treatment) in later months. AP use may merely be a marker for the presence of cardiovascular risk factors and not the reason for MI; alternately, APs may interact with state-dependent risk factors through unknown mechanisms to trigger MI. With regards to the non-significant elevation (Brauer et al., 2015; Pariente et al., 2012) in the risk of MI in long-term APs users, since the development of atherosclerotic plaque takes a period of years to decades, the mean follow-up time from participants in the analyzed cohort studies (approximately 6.5 years with the range of 1-13 years)(Enger et al., 2004; Hwang et al., 2014; Pariente et al., 2012; Pratt et al., 1996) may be insufficient for AP to meaningfully affect the MI process. Therefore, our results tend to reflect relatively short-term effects of AP use.

## Mechanism

Mechanisms of MI risk and exposure to APs remains unclear. Since a



shorter-term relationship for MI risk during the first 2 month of treatment was shown in our analysis, this result might indicate other vascular processes (Pariante et al., 2012) or conduction deficits, as have been proposed as potential causes of sudden cardiac death(Wang et al., 2007; Suvisaari et al., 2010). Our results also suggest that patients experience an MI early on in the treatment, independent of a history of CVD and age, which could point to a triggering effect caused by APs. Similar results were found in one previous study (Brauer et al., 2015). Potential pharmacological mechanisms might include venous thromboembolism, affinity of APs to D3-dopamine, and 5-HT-serotonin receptors as has been discussed in previous literature (Jonsson et al., 2012; Lin et al., 2014; O'Brien and Oyebode, 2003). Based on a meta-analysis of 17observational studies (Barbui et al., 2014), APs were concluded to be associated with a50% increased risk of venous thromboembolism. Excessive activation of platelets may be involved in MI, stroke, and increased risk of thrombotic complications and might be causes of morbidity and mortality in AP users.

Furthermore, the D3-dopamine receptor has been implicated in the pathogenesis of MI in relation to plaque rupture and platelet aggregation(Ricci et al., 2001) in animal studies. One study (Lin et al., 2014) of the selected binding of APs to 14 neurotransmitter receptors revealed only D3-dopamine receptor antagonism to be significantly associated with MI risk. The higher MI risk observed in AP users with

schizophrenia in our study is consistent with the possibility that, in addition to unhealthy lifestyle, autonomic nervous system dysfunction triggered by schizophrenia may be exacerbated by AP treatment through blockade of peripheral dopamine receptors, increasing sympathetic activity (Scigliano and Ronchetti, 2013). Most atypical APs are serotonin receptor antagonists, and 5-HT-serotonin activity represents another possible link with coronary artery diseases. Specifically, activated platelets release large amount of serotonin which participates in cardiac remodeling through the regulation of endothelial and vascular smooth muscle cells, potentially responsible for atherosclerosis (Yabanoglu et al., 2009). Although AP use has a time-dependent effect on MI risk, a plethora of recent work from investigators such as Tiihonen et al. (2011) have reported that AP treatment is associated with lower mortality (adjusted HR 0.45, 95% CIs 0.31–0.67) than no AP use. As APs are effective in treating some severe mental illness, the relatively small increased risk of MI is unlikely to alter their benefit-risk balance.

## Limitation

In drawing conclusions, it is important to bear in mind that non-randomized data are susceptible to selection bias and residual confounding. Inadequate control for

confounders may bias the results in either direction: towards exaggeration or underestimation of risk estimates. This study is limited in several ways, which should be taken into account when interpreting these data. First, inconsistencies in study designs, sample sizes, and participants' baseline characteristics were found across studies. For the case-control studies, we cannot rule out the possibility of recall bias. The case-crossover and self-controlled case series studies reduce the possibility of between-individual time-invariant confounding (as individuals are their own controls) and were more suitable to investigate short-term effects of exposures on acute outcomes. Second, each observational study adjusted for different confounding factors. Most studies we analyzed failed to account for one or more of the following risk factors for MI: smoking, physical inactivity, obesity, and poor diet. All of which might well vary disorder severity, and therefore affect pharmacotherapy received. Third, most studies included in this meta-analysis comprised different populations. These populations might be different in baseline MI risk. Hence, subgroup analyses were conducted based on different study designs and populations to investigate potential sources of heterogeneity. Besides, a higher MI risk and lower heterogeneity were seen in case-crossover studies and in samples with schizophrenia. Fourth, the use of filled prescriptions to capture exposure information does not allow the ascertainment of the participants' compliance, and disease and outcome measures

based on diagnostic codes may lack clinical information, such as that on disease duration and severity, indication for AP use, and social supports, all of which might be related to AP choice. Fifth, this analysis collated individual drugs into typical and atypical classes, although effects and adverse reactions may differ between agents within a single class. Only one study provided data on MI risk associated with individual APs (Lin et al., 2014), finding the highest risk with amisulpiride (OR 5.65, 95% CIs 2.97-10.76). However, another study conducted by Sahlberg et al. (2015) found that the incidence of major adverse cardiovascular events (comprised the first occurring nonfatal MI) was higher with use of levomepromazine (RR 3.80, 95% CIs 3.43-4.21) and haloperidol (RR 1.85, 95% CIs 1.67-2.05) and lower for treatment with flupentixol (RR 0.54, 95% CIs 0.45-0.66) and chlorprothixen (RR 0.76, 95% CIs 0.61-0.95) compared with risperidone. While the increased MI risk similarly applies to typical and atypical APs as previously reported (Huybrechts et al., 2012; Jackson et al., 2015; Wang et al., 2009), differences between typical and atypical agents were observed in one direct comparison (Vasilyeva et al., 2013) which found higher MI risk in people using atypical APs. Inconsistent findings might reveal the heterogeneity in receptor-binding profiles among typical and atypical APs and further research on individual drugs might still be needed. Finally, dose-response relationships between AP use and the risk of MI analyses could not be investigated because of insufficient

data.

Despite the limitations, it raises awareness of safety issues associated with AP treatment. Where no RCTs exist, observational studies may be the only recourse. Golder et al. (2011) had reported that there is no difference on average in the risk estimate of an intervention's adverse effects obtained from meta-analyses of RCTs and from meta-analyses of observational studies. Our study has strengths in that it included a large number of people who were taking APs in a real-life setting, drawn from a data resource with near-universal national coverage. Large, nation-wide samples provide statistical power advantages.

## **Conclusion**

The present meta-analysis, consisting of four case-control, two case-crossover, one case-case time control, four cohort, and two self-controlled case series studies, indicates a significantly increased MI risk in any, atypical and typical AP users compared with non-users. Subgroup analyses indicate that male patients, those with schizophrenia, and those with AP exposure periods  $\leq 60$  days are more likely to develop MI. However, caution is needed in interpreting the findings from our results because of the high heterogeneity between studies. Findings on MI risk need to be

viewed in the wider context of lower mortality associated with AP treatment in severe mental illness. Instead of suggesting not using APs, the implication would be that these high-risk patients group should receive close monitoring before and during AP use. More studies are warranted to identify other possible intervening conditions and hence potentially vulnerable subpopulations.

### **Funding**

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. RS is part-funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London

### **Declaration of interest**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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